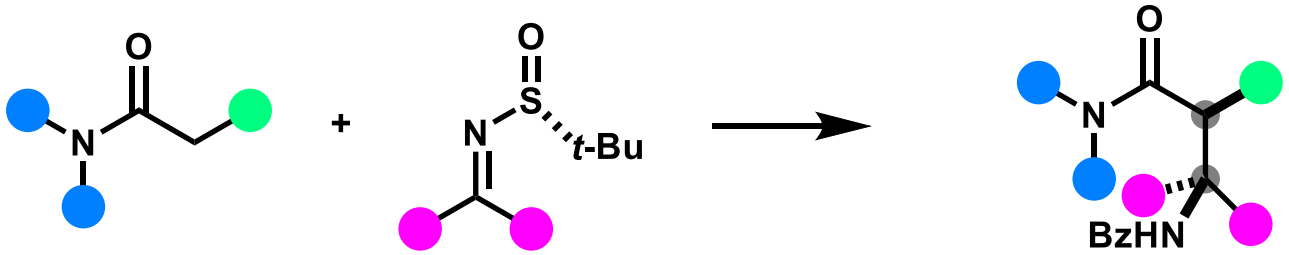
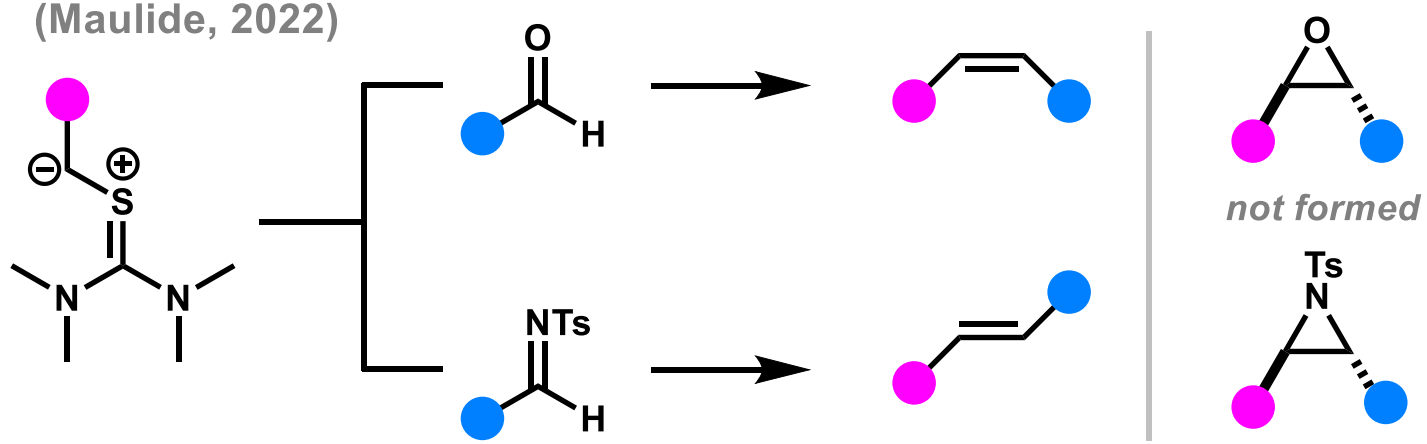
Surrogate Asymmetric Mannich Reaction with Sulfinimines and Stereodivergent Olefination with Sulfur Ylides by Nuno Maulide's group

2022/8/27 Yuya Shiga

Contents





Nuno Maulide

2003-2004 : Master's Degree, the Ecole Polytechnique

2004-2007 : Ph. D, the Université catholique de Louvain (Prof. István E. Markó)

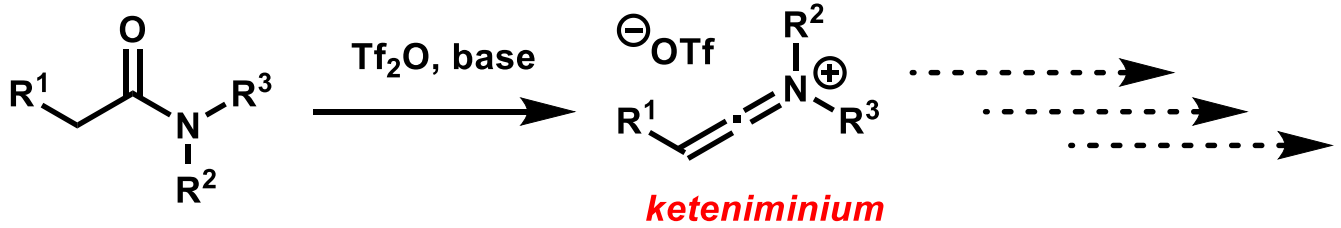
2007-2008 : Postdoc, Stanford University (Prof. Barry M. Trost)

2009-2013 : Group Leader, Max-Planck Institute for Coal Research

2013- : Full Professor, the University of Vienna

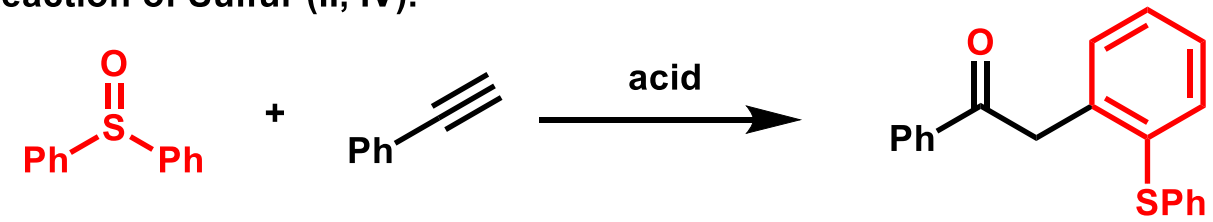
Reseach Topic:

1. Activation of amides or ynamides.



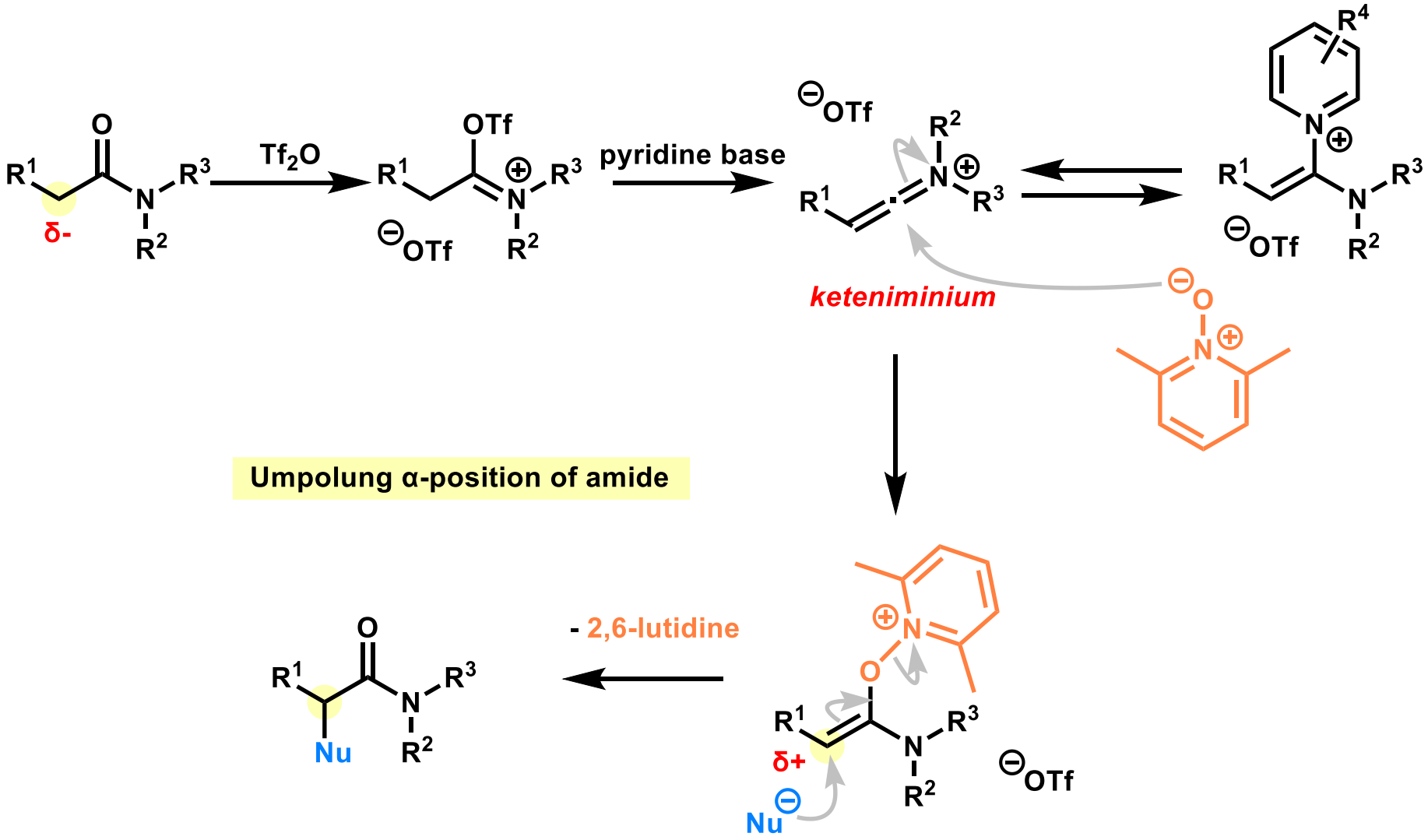
keteniminium

2. Reaction of Sulfur (II, IV).



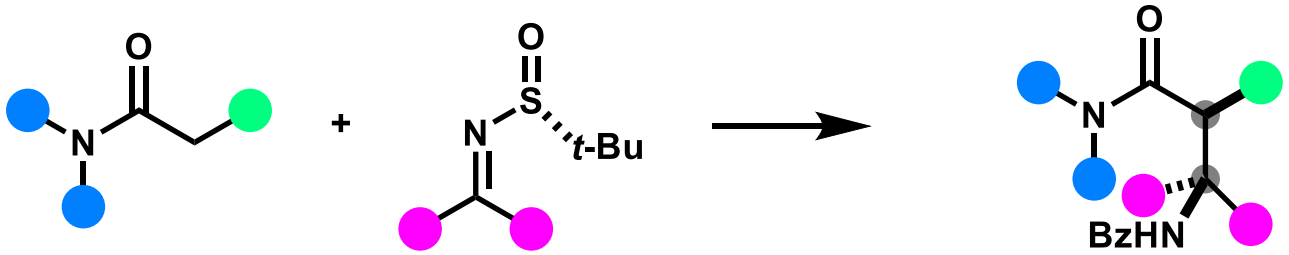
3. Total Synthesis

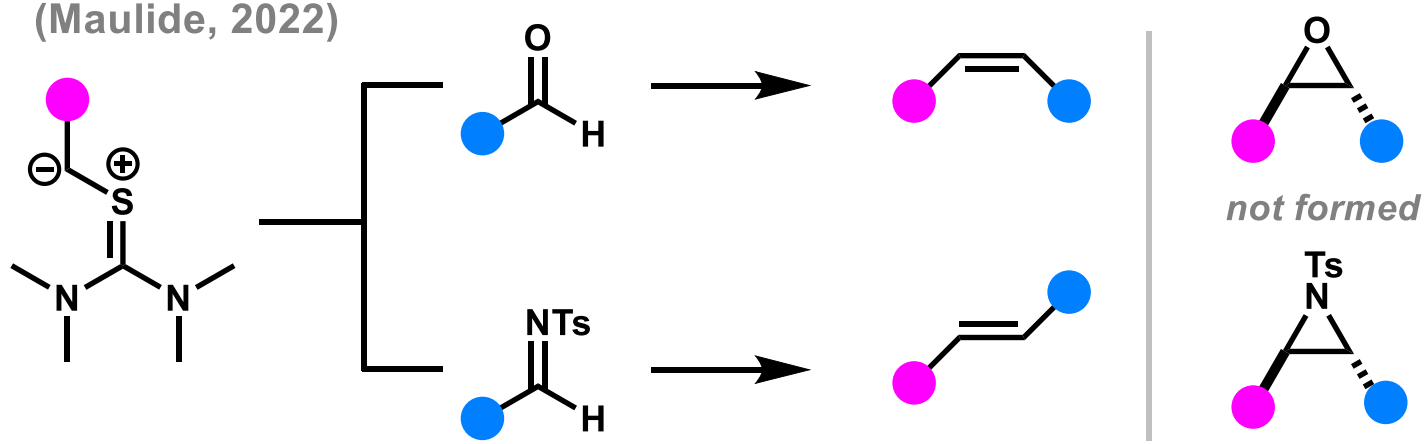
Activation of Amide via Keteniminium



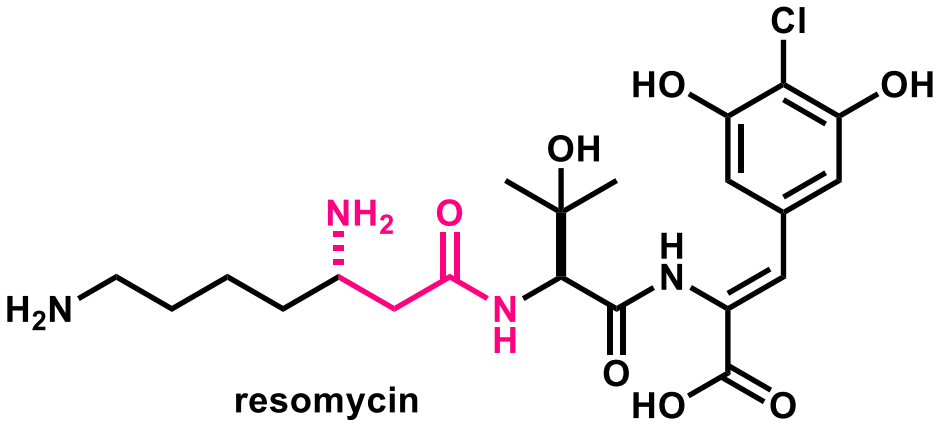
1) Kudo, F.; Miyanaga, A.; Eguchi, T. *Nat. Prod. Rep.* **2014**, *31*, 1056.

Contents

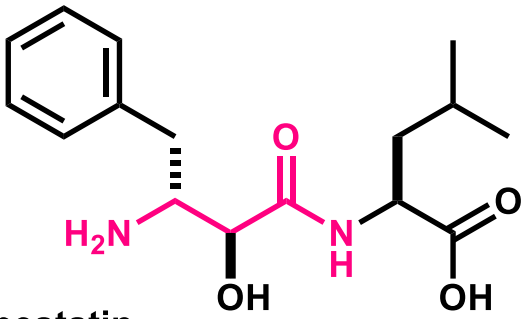




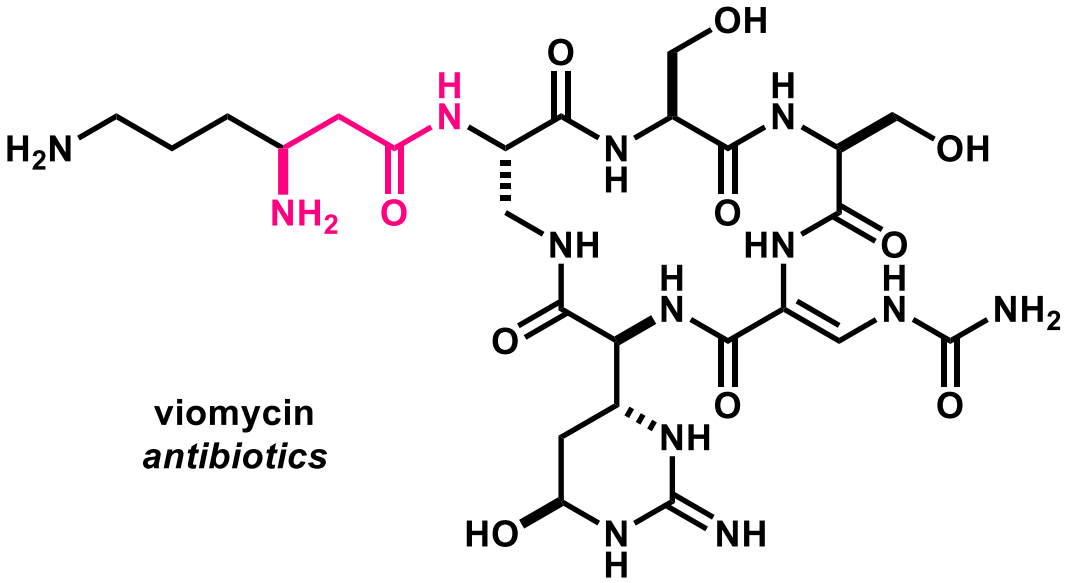
β-Amino Acids as Natural Products and Drug Scaffolds



resomycin
herbicidal antibiotics



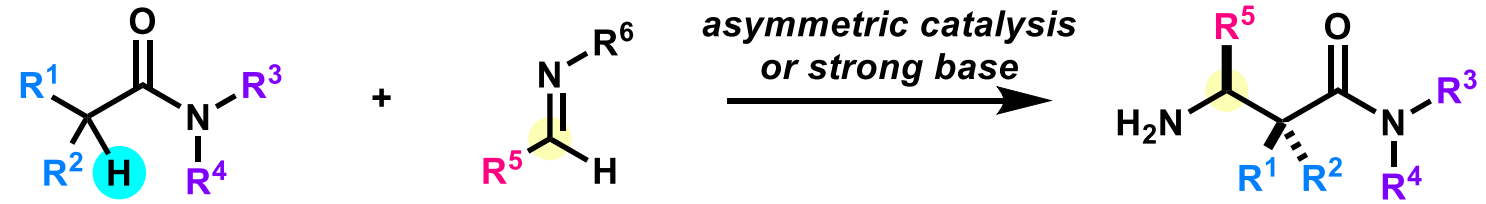
bestatin
protease inhibitor



viomycin
antibiotics

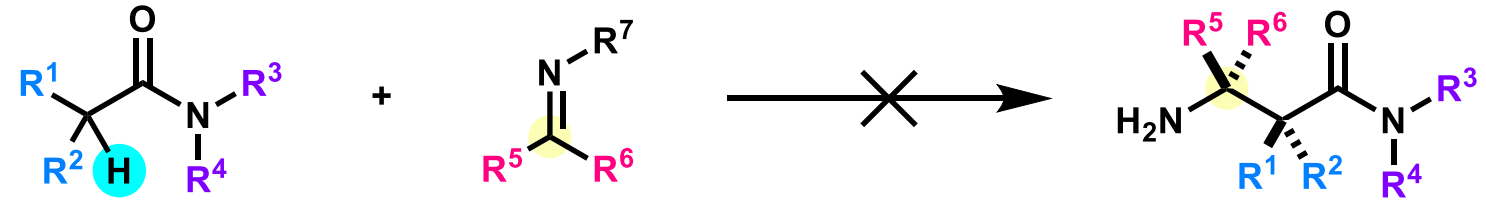
1) Kudo, F.; Miyanaga, A.; Eguchi, T. *Nat. Prod. Rep.* **2014**, *31*, 1056.

Classical Mannich Reaction for the Construction of β-Amino Amides



*p*Ka = ~35

aldimines



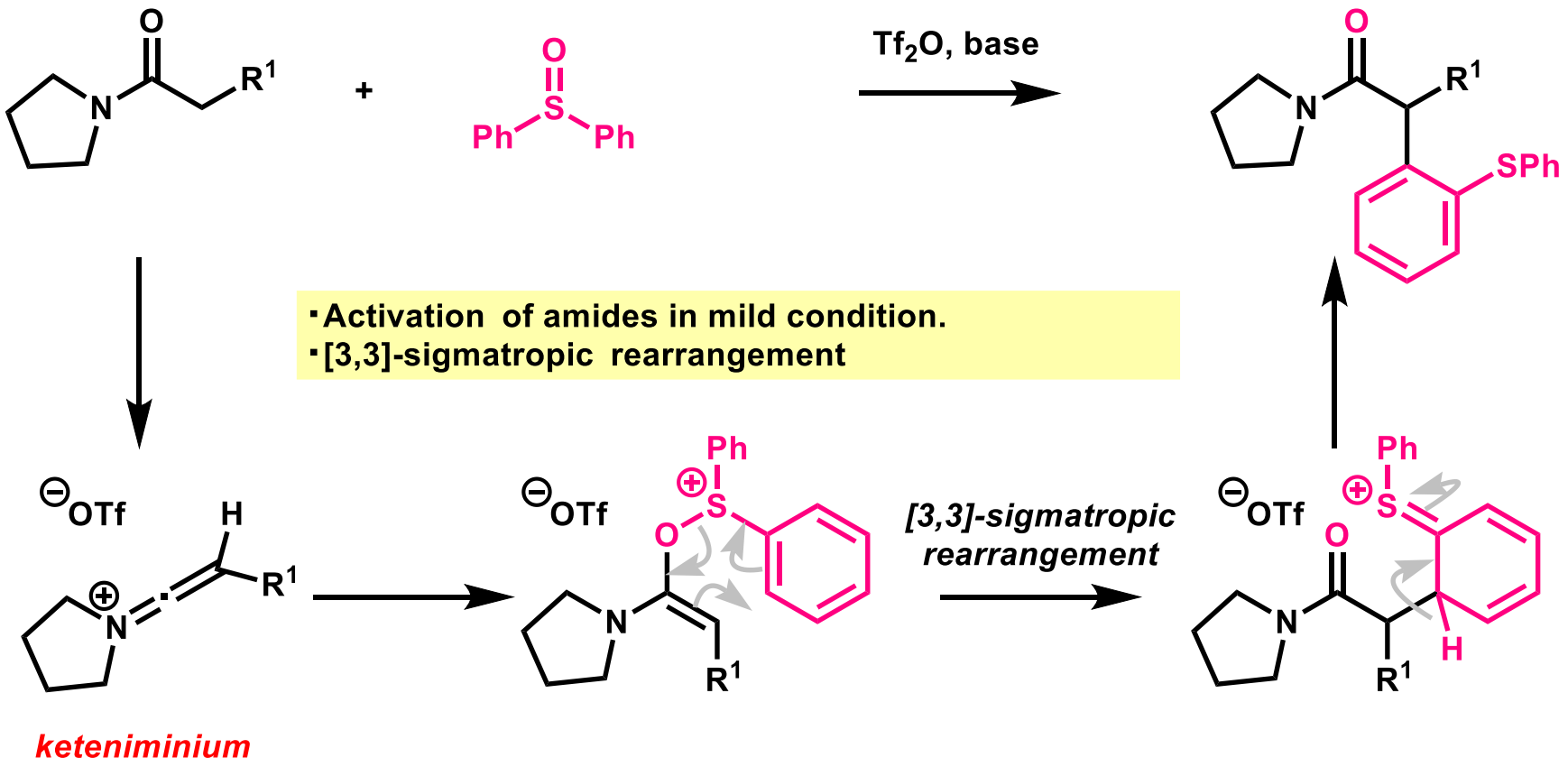
*p*Ka = ~35

ketimines

- Strong base is required
- The construction of quaternary carbon is unsolved.

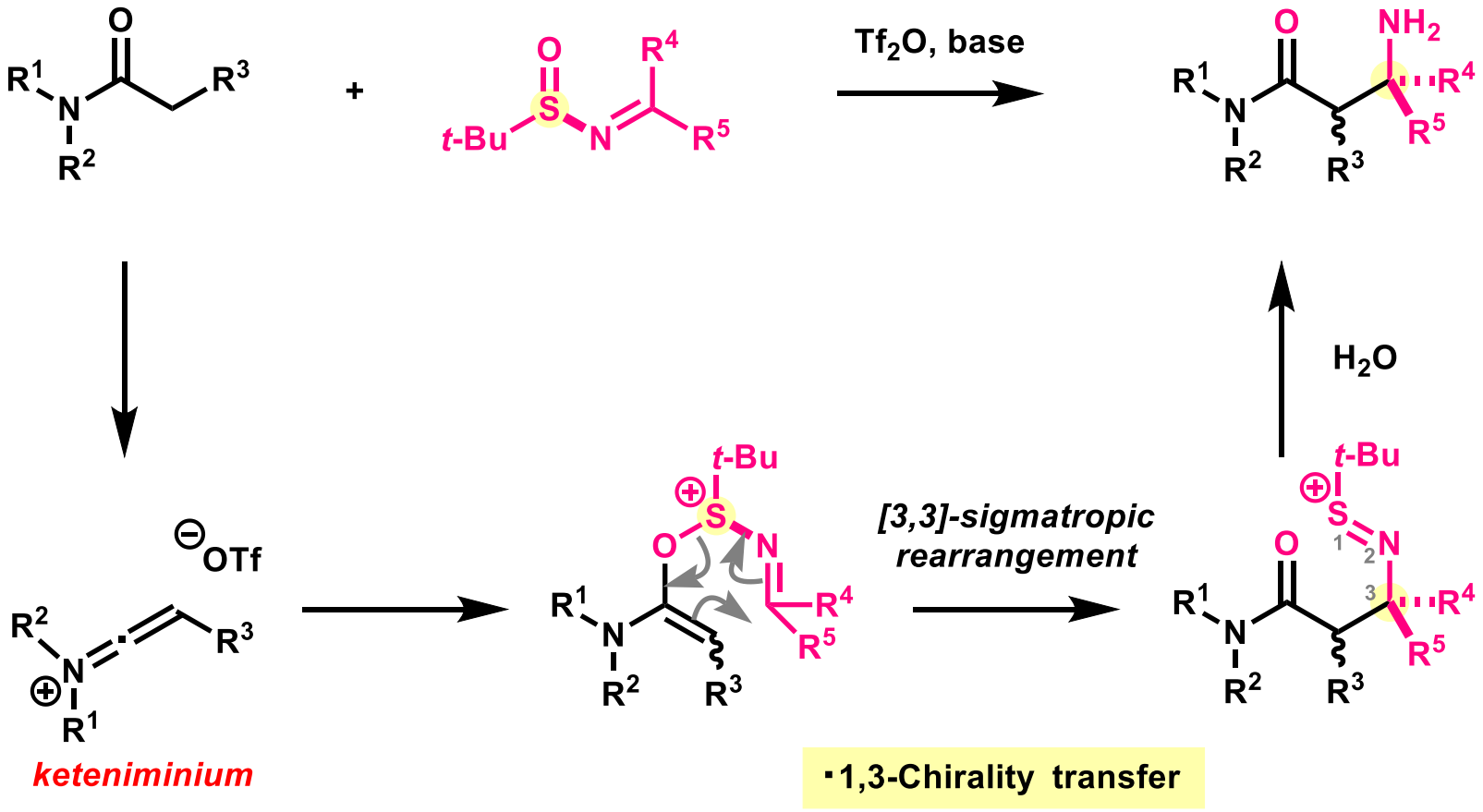
1) Yin, L.;Brewitz, L.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2014**, *136*, 17958. 2) Sun, B.; Balaji, P. V.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2017**, *139*, 8295.

α-Arylation of Amides by Sulfonium Rearrangement



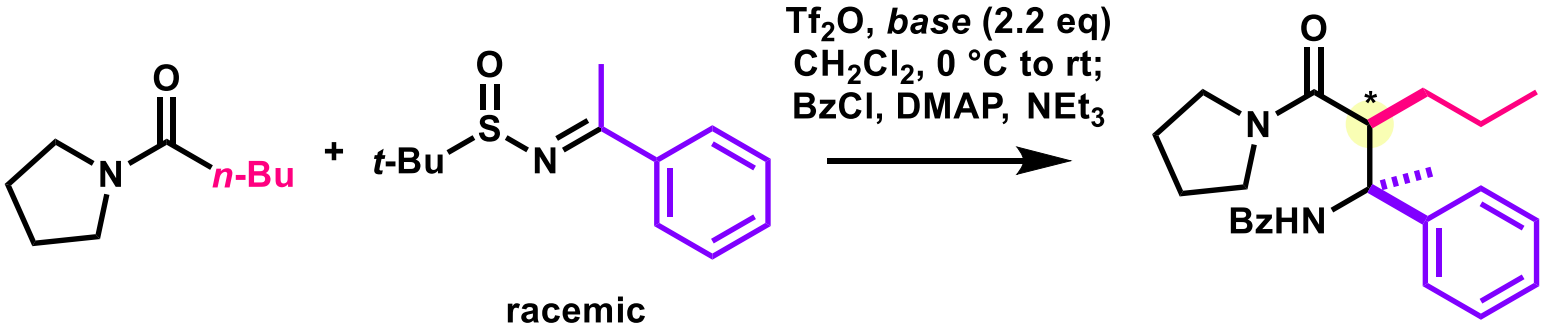
1) Huang, X.; Klimczyk, S.; Maulide, N. *Synthesis* **2012**, *2012*, 175.

A Sulfonium Rearrangement Approach for the Construction of β-Amino Amides

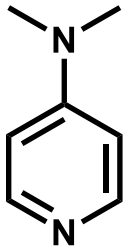


1) Feng, M.; Mosiagin, I.; Kaiser, D.; Maryasin, B.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 13044.

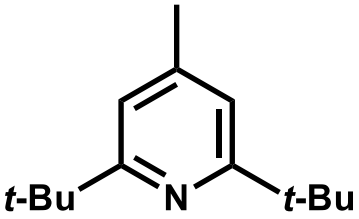
Optimization of the Reaction Conditions



entry	*base*	yields	d.r.*
1	2,6-Di-*t*-butyl-4-methylpyridine	trace	-
2	2-Ph-pyridine	36%	7:1
3	2-Me-pyridine	50%	10:1
4	2-OEt-pyridine	73%	10:1
5*	2-OEt-pyridine	55%	10:1



DMAP

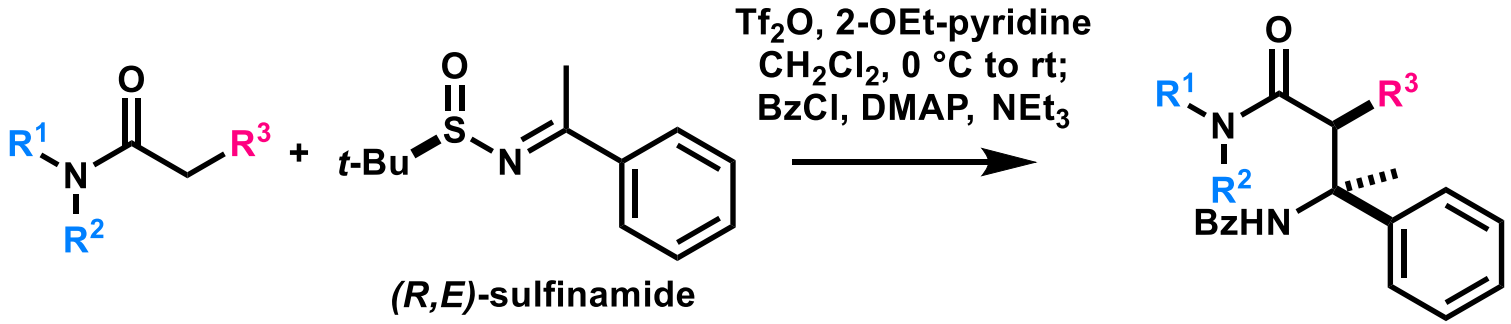


2,6-Di-*t*-butyl-4-methylpyridine

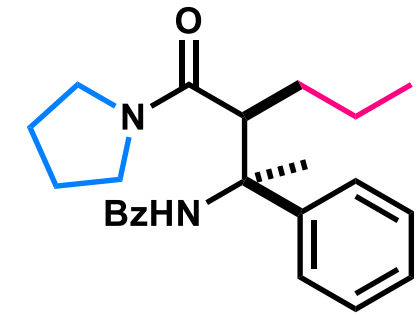
* 3.0 equivalents of sulfonimine were used.

1) Feng, M.; Mosiagin, I.; Kaiser, D.; Maryasin, B.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 13044.

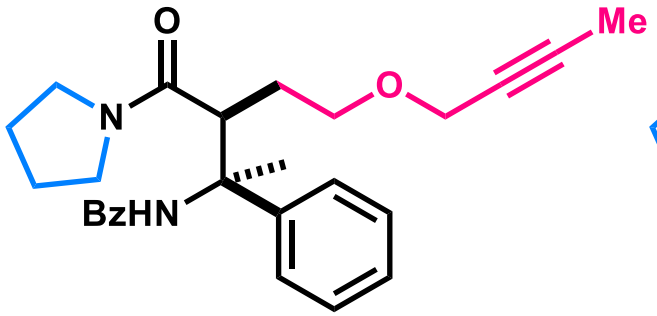
Substrate Scope (I)



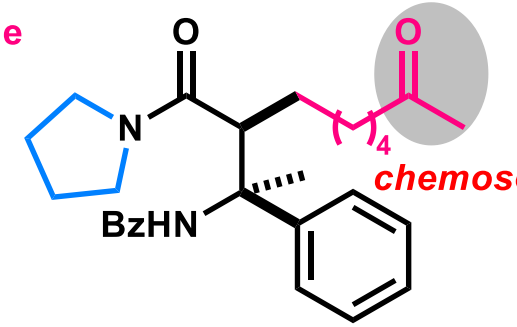
(R,E)-sulfinamide



73%, 10:1 d.r., 99.9:0.01 e.r.

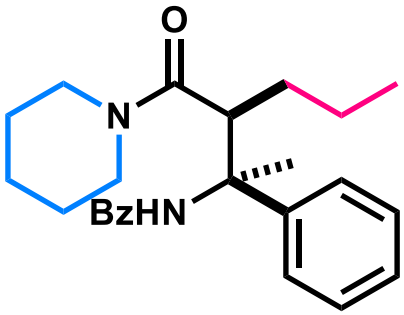


46%, 11:1 d.r., 91:9 e.r.

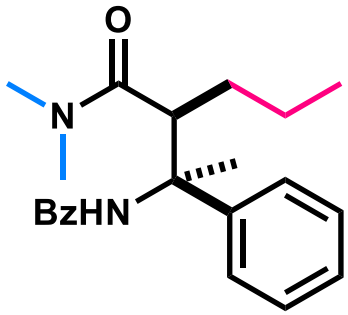


chemoselective

50%, 5:1 d.r., 94:6 e.r.



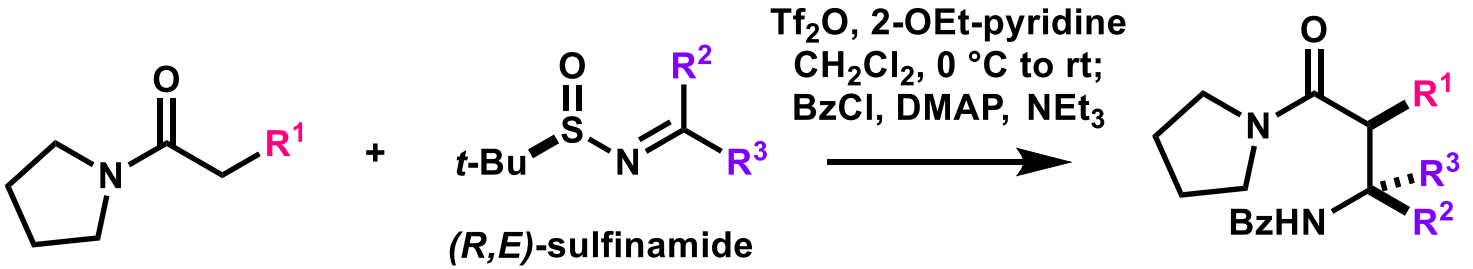
50%, >20:1 d.r., 90:10 e.r.

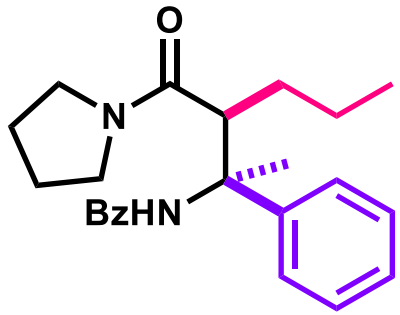


44%, >20:1 d.r., 91:9 e.r.

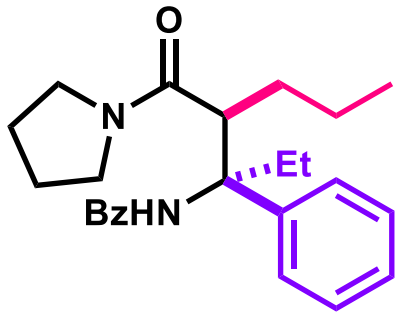
1) Feng, M.; Mosiagin, I.; Kaiser, D.; Maryasin, B.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 13044.

Substrate Scope (II)

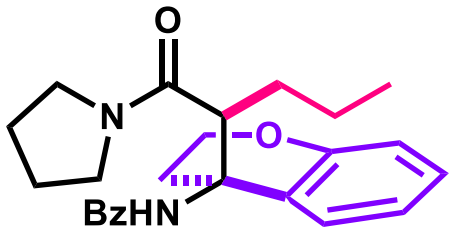




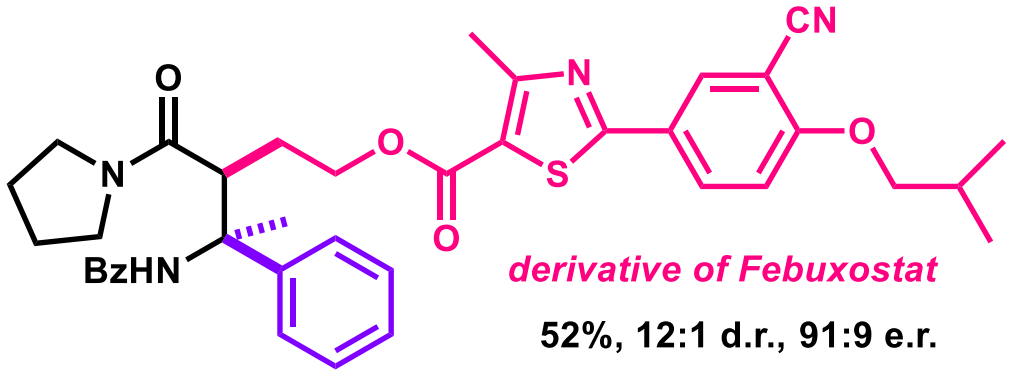
73%, 10:1 d.r., 99.9:0.01 e.r.



29%, 12:1 d.r., 99.8:0.2 e.r.



55%, >20:1 d.r., 98:2 e.r.

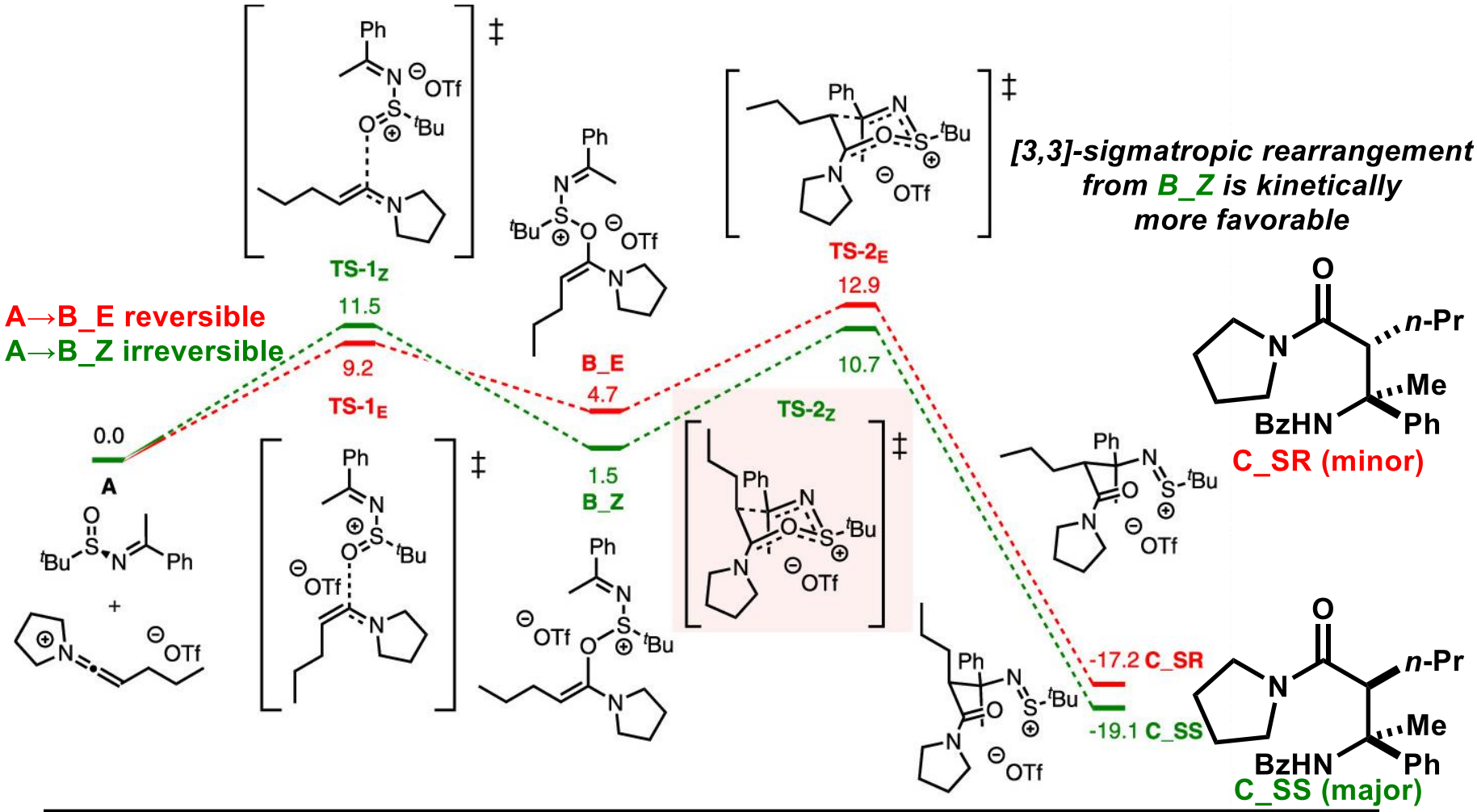


derivative of Febuxostat

52%, 12:1 d.r., 91:9 e.r.

1) Feng, M.; Mosiagin, I.; Kaiser, D.; Maryasin, B.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 13044.

Mechanistic Insight into the Diastereoselectivity

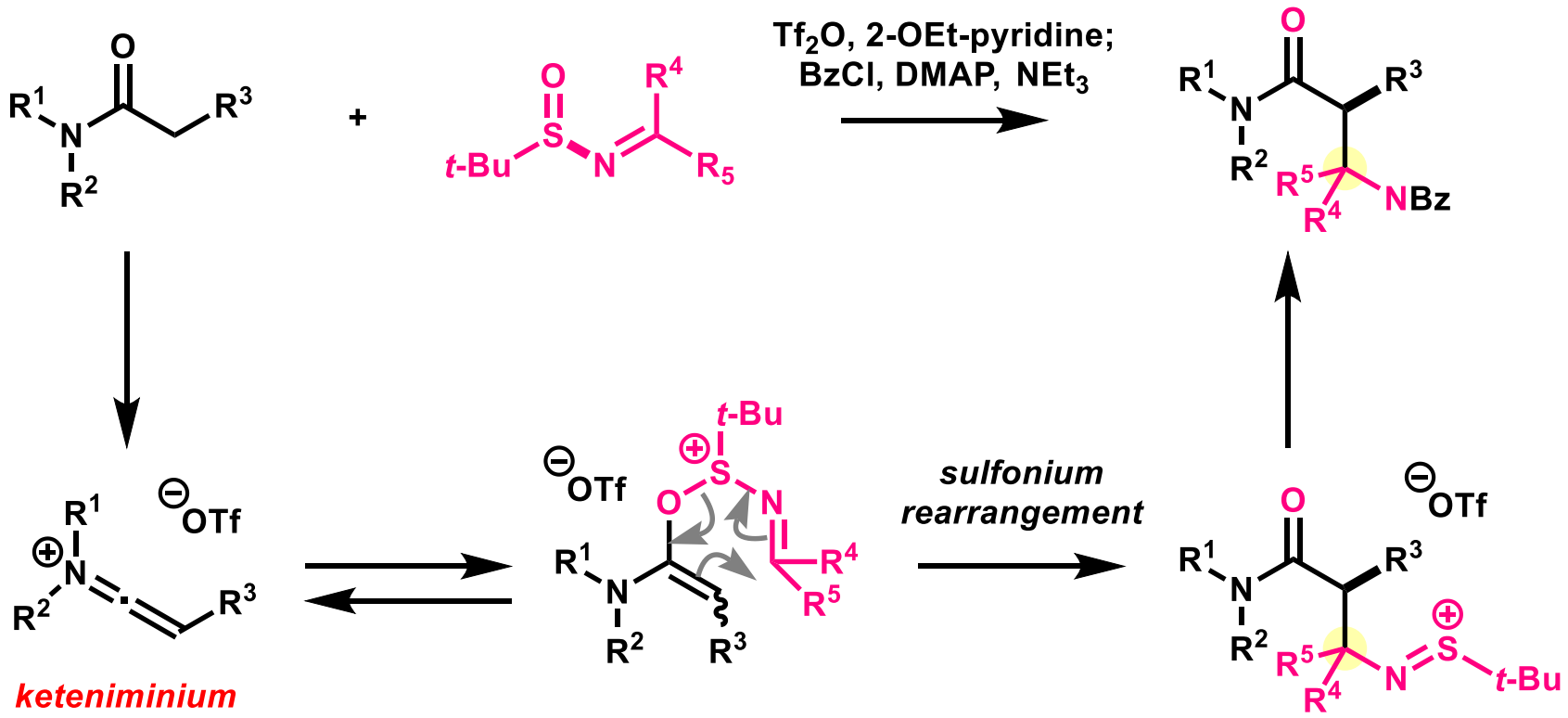


The diastereoselectivity is determined by the Z/E isomerism of the transient intermediate B.

Calculations were conducted at DLPNO−CCSD(T)/def2-TZVP//B3LYP-D3(BJ)/def2-SVP level of theory

1) Feng, M.; Mosiagin, I.; Kaiser, D.; Maryasin, B.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 13044.

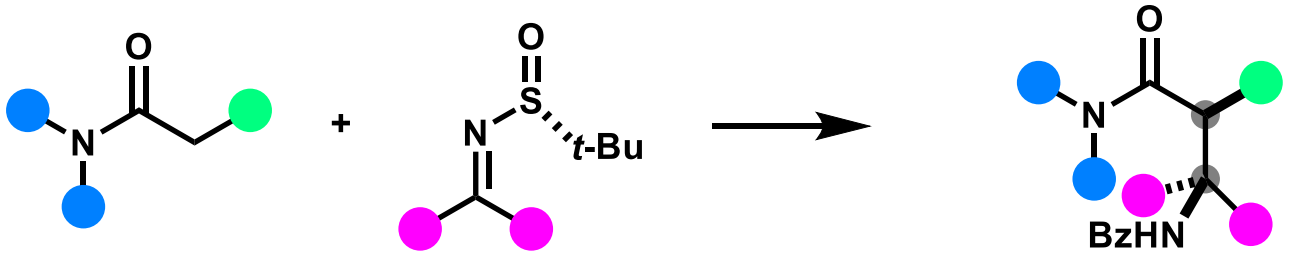
Summary 1

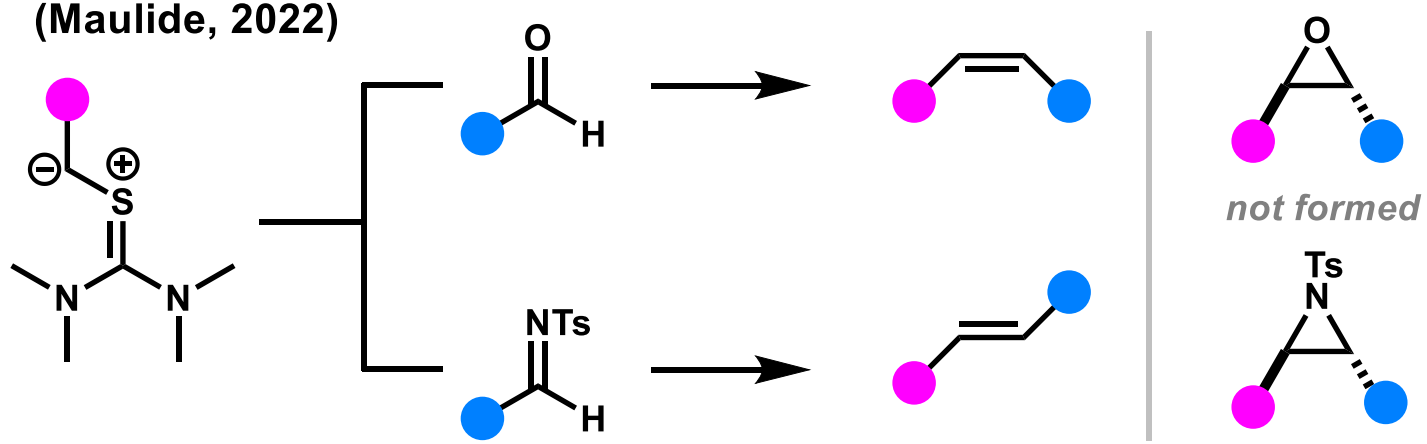


- surrogate asymmetric mannich reaction
- quaternary stereocenters
- high diastereo- and enantioselective
- high functional-group tolerance

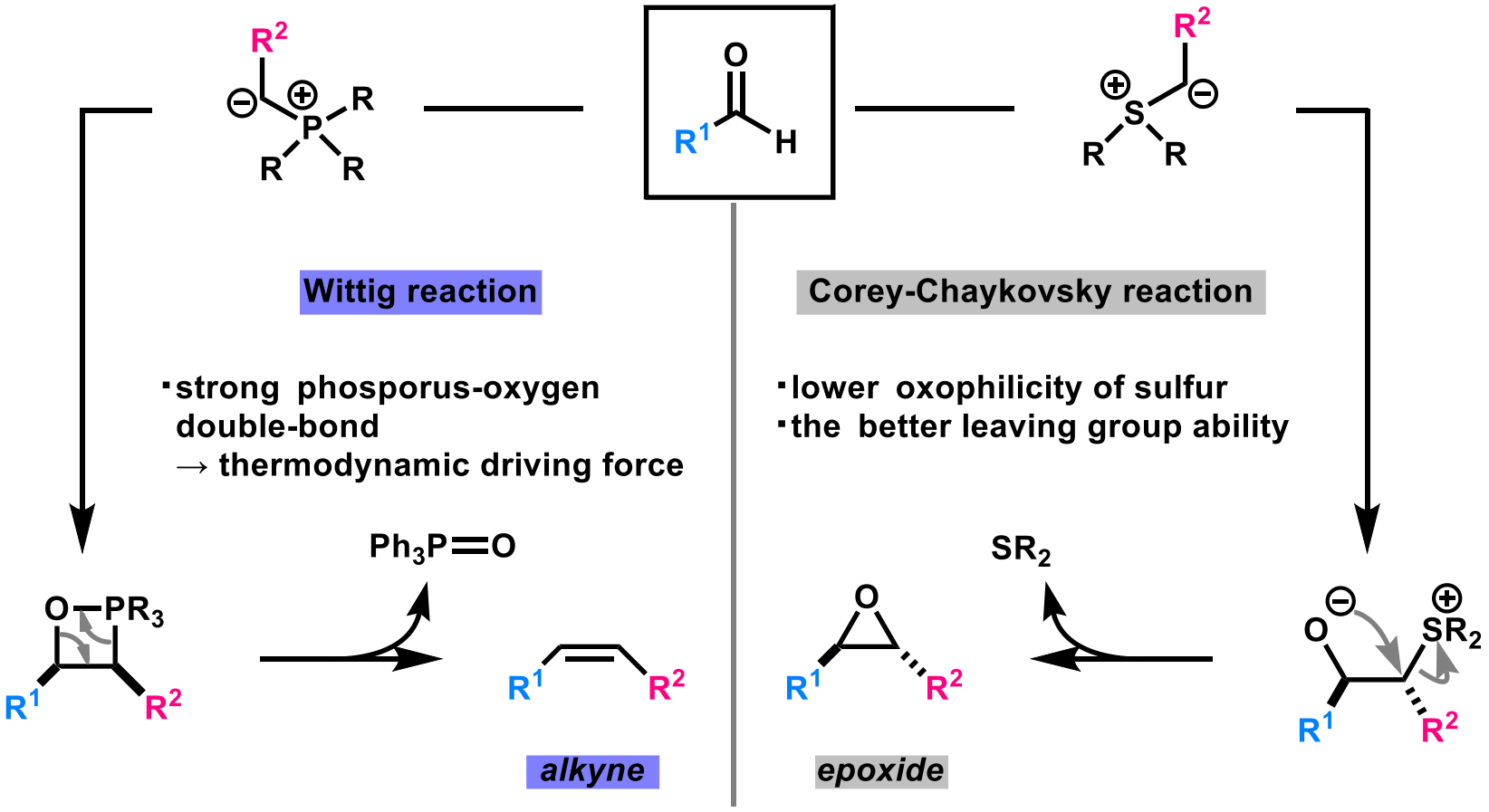
1) Merad, J.; Grant, P.;Stopka, T.; Sabbatani, J.; Meyrelles, R.; Preinfalk, A.; Matyasovsky, J.; Maryasin, B.; Gonzalez, L.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 12536.

Contents



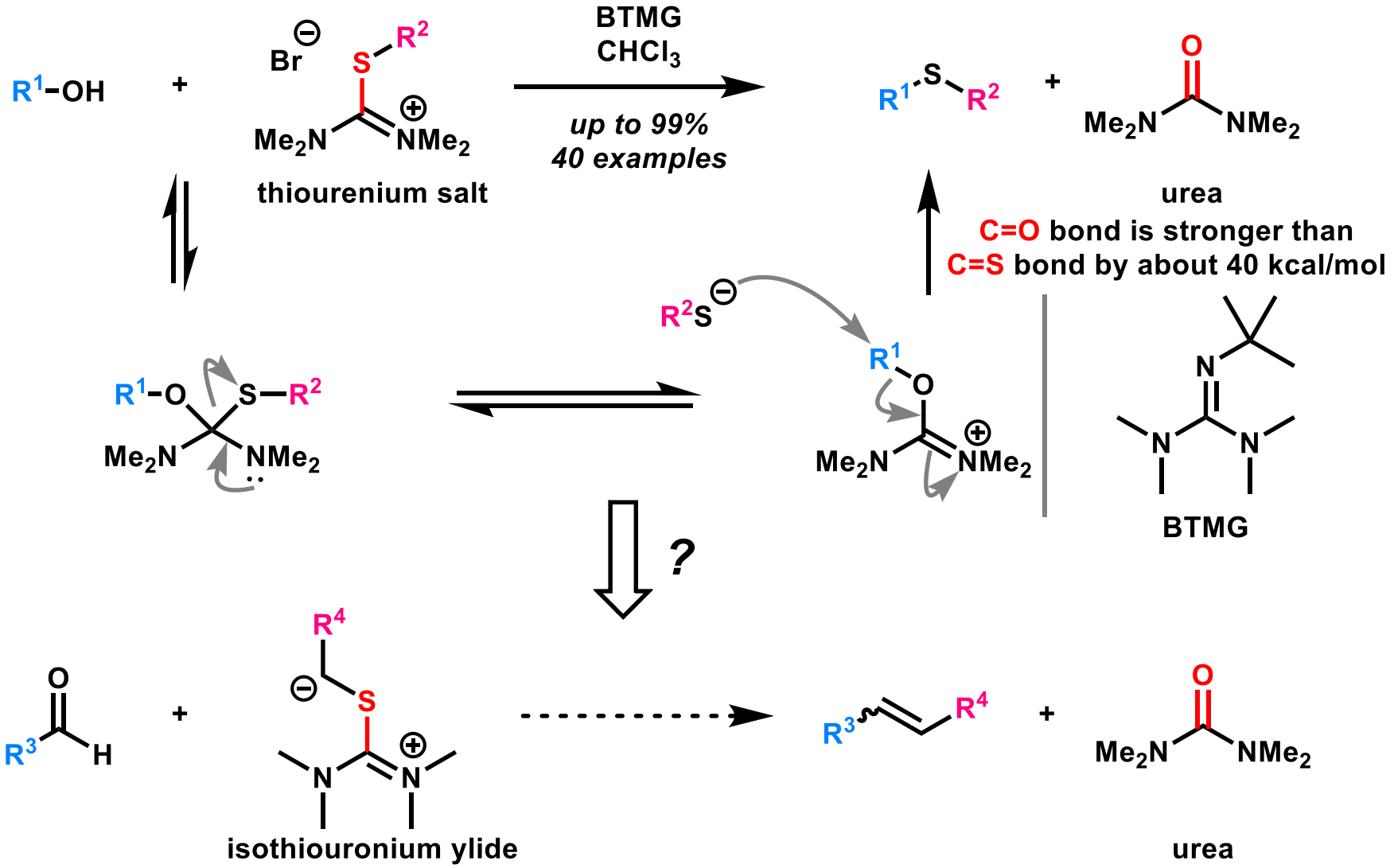


P- and S-ylides: A Textbook Reactivity Dichotomy



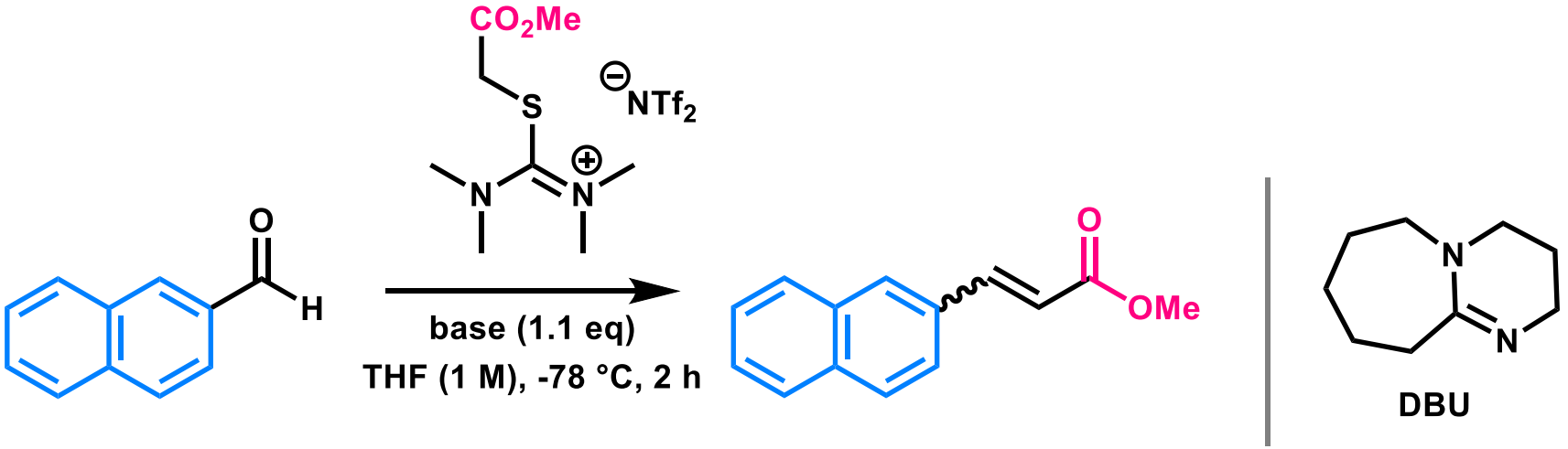
Is it impossible to proceed olefination by S-ylide?

Previous Works about Thiouronium Salts



1) Merad, J.; Matyasovsky˘, J.; Stopka, T.; Brutiu, B. R.; Pinto, A.; ´Drescher, M.; Maulide, N. *Chem. Sci.* **2021**, 12, 7770. 2) Hadad, C. M.; Rablen, P. R.; Wiberg, K. B. *J. Org. Chem.* **1998**, *63*, 8668.

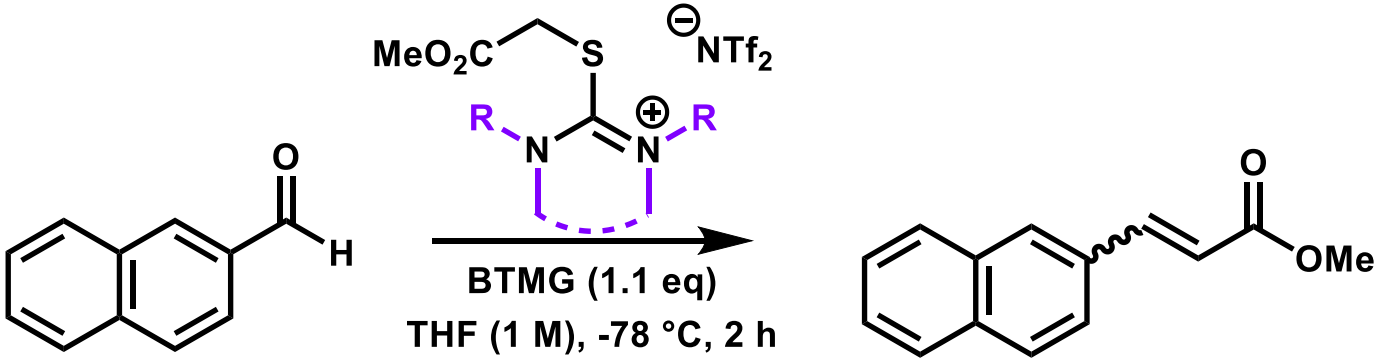
Optimization for the Reaction Conditions

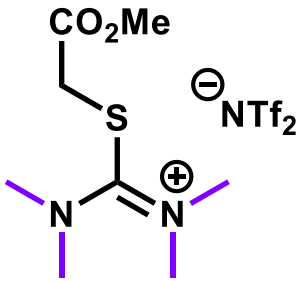


entry	base	slolvent	olefin (E:Z)
1	$KNTMS_2$	THF	93% (1.3/1)
2	$LiN(i\text{-}Bu)_2$	THF	91% (1.2/1)
3	NEt_3	THF	not observed
4	DBU	THF	55% (1/2.6)
5	BTMG	THF	93% (1/3.6)
6	BTMG	CH_2Cl_2	90% (2.2/1)

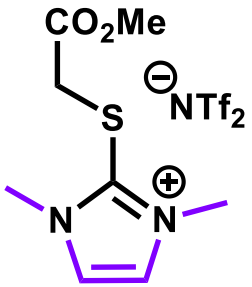
1) Merad, J.; Grant, P.;Stopka, T.; Sabbatani, J.; Meyrelles, R.; Preinfalk, A.; Matyasovsky, J.; Maryasin, B.; Gonzalez, L.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 12536.

Optimization of Isothiouronium Bistriflimides

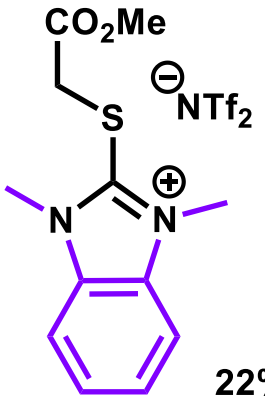




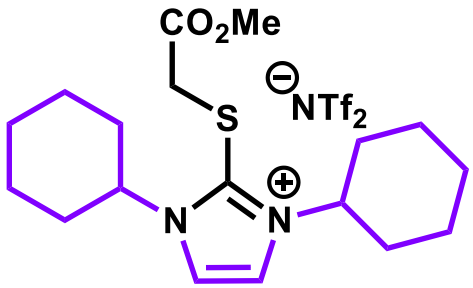
93% (E:Z=1/3.6)



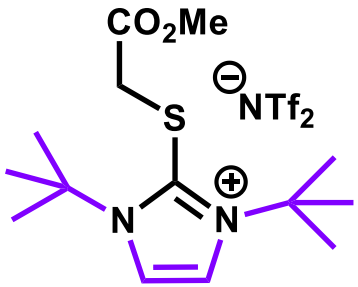
97% (E:Z=1/2.8)



22% (E:Z=1/1.5)



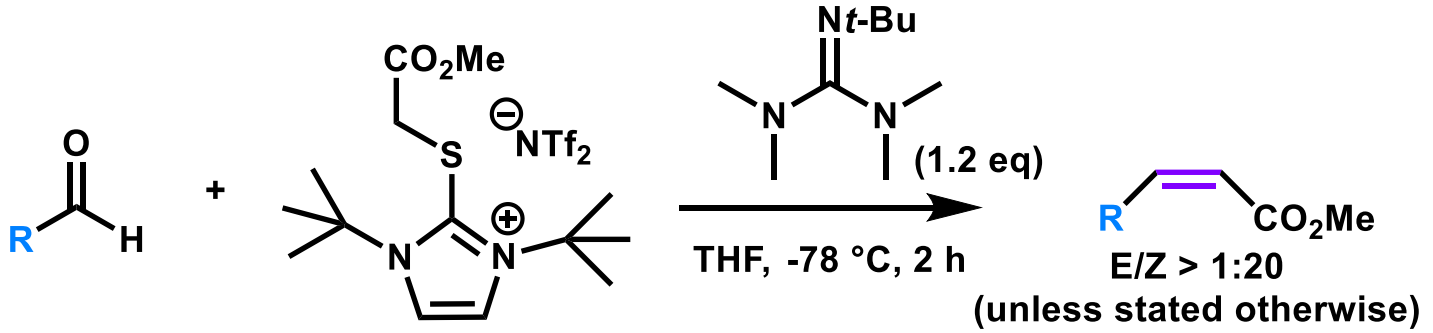
60% (E:Z=1/18)



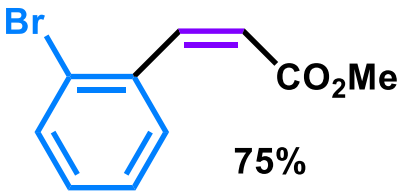
92% (only Z)

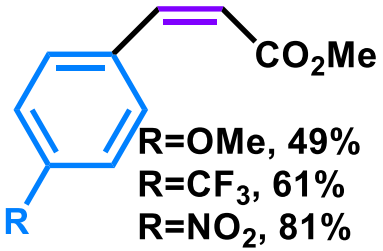
1) Merad, J.; Grant, P.;Stopka, T.; Sabbatani, J.; Meyrelles, R.; Preinfalk, A.; Matyasovsky, J.; Maryasin, B.; Gonzalez, L.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 12536.

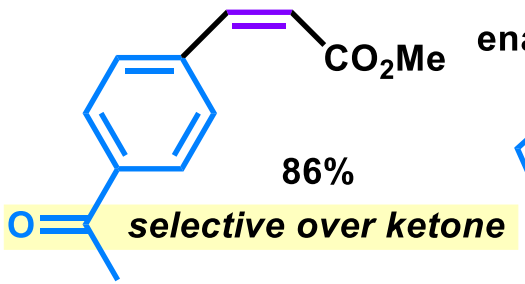
Substrate Scope (I)



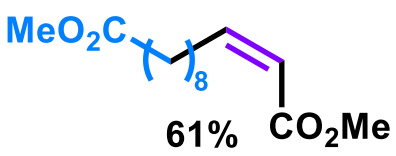
aryl aldehydes

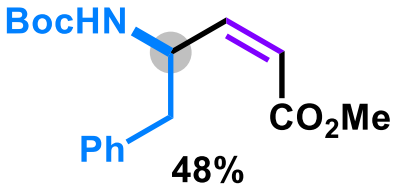






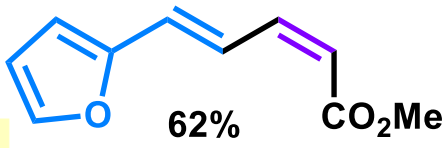
aliphatic aldehydes



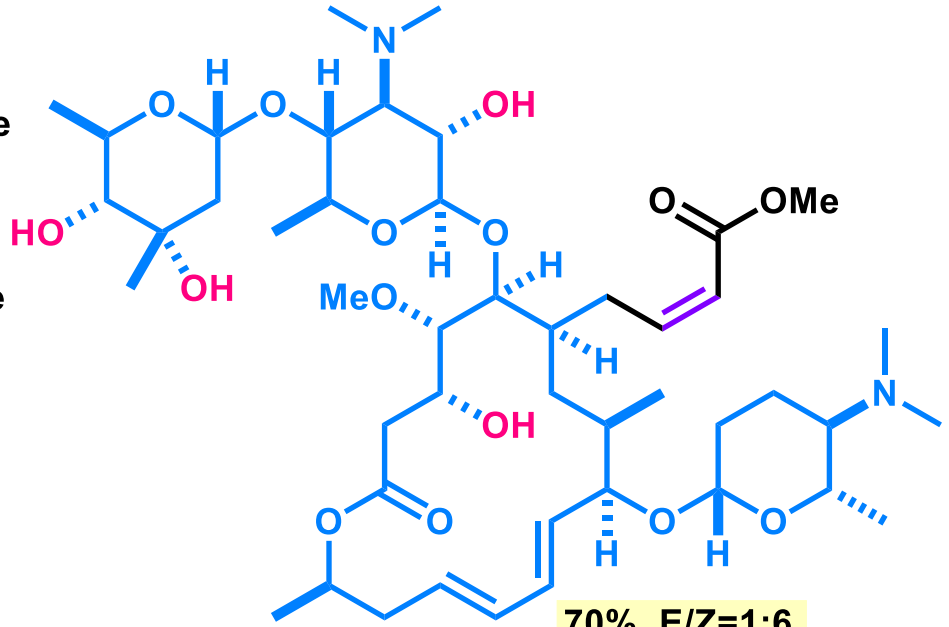


no rasemisation

enal



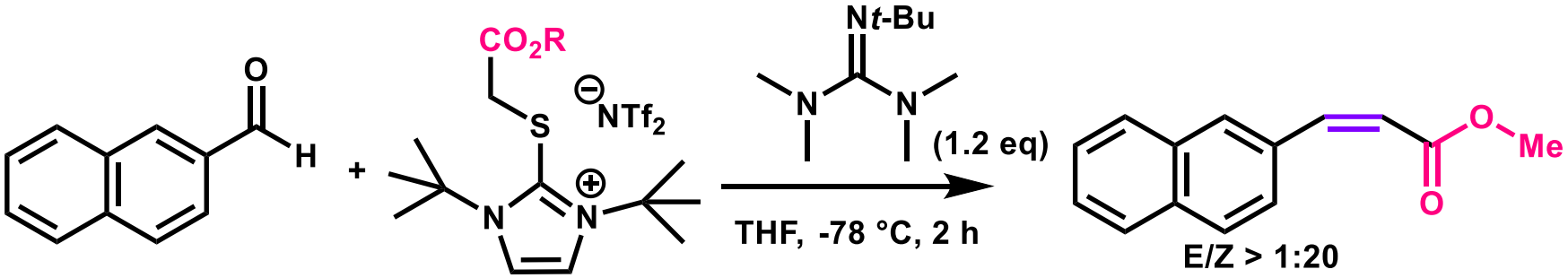
complex *unprotected* macrolide antibiotic

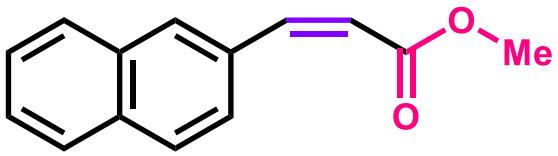


70%, E/Z=1:6
Still-Gennari
E/Z=1:1.7

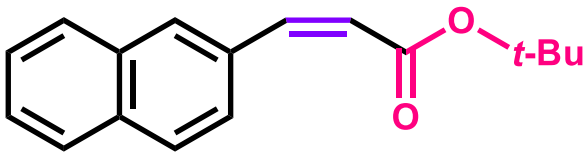
1) Merad, J.; Grant, P.;Stopka, T.; Sabbatani, J.; Meyrelles, R.; Preinfalk, A.; Matyasovsky, J.; Maryasin, B.; Gonzalez, L.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 12536.

Substrate Scope (II)

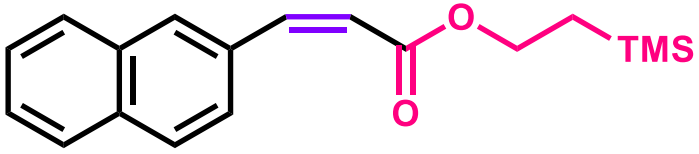




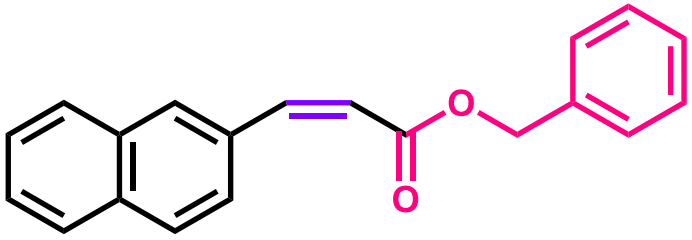
92%
(88% gram scale)



83%



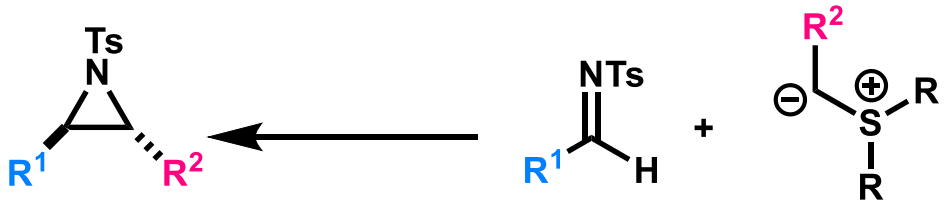
84%



85%

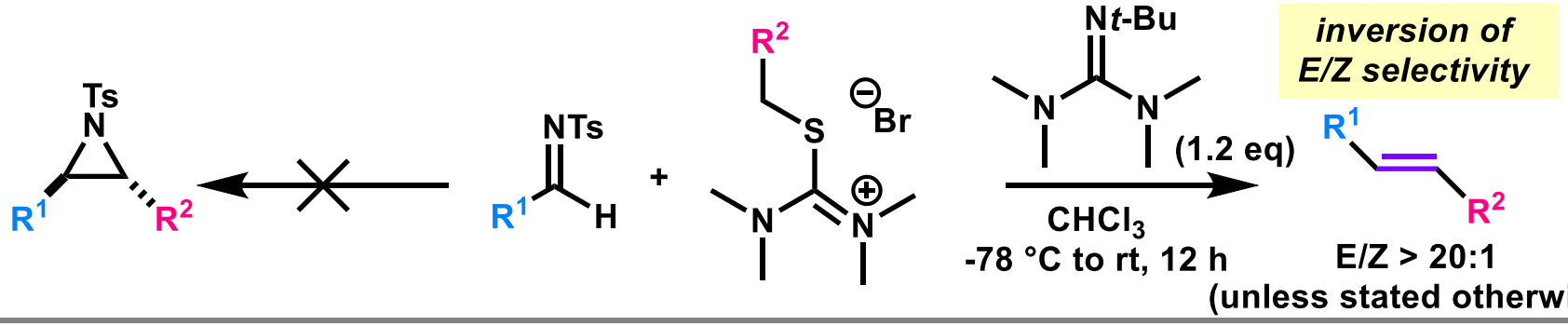
1) Merad, J.; Grant, P.;Stopka, T.; Sabbatani, J.; Meyrelles, R.; Preinfalk, A.; Matyasovsky, J.; Maryasin, B.; Gonzalez, L.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 12536.

Reaction of N-Tosylimines

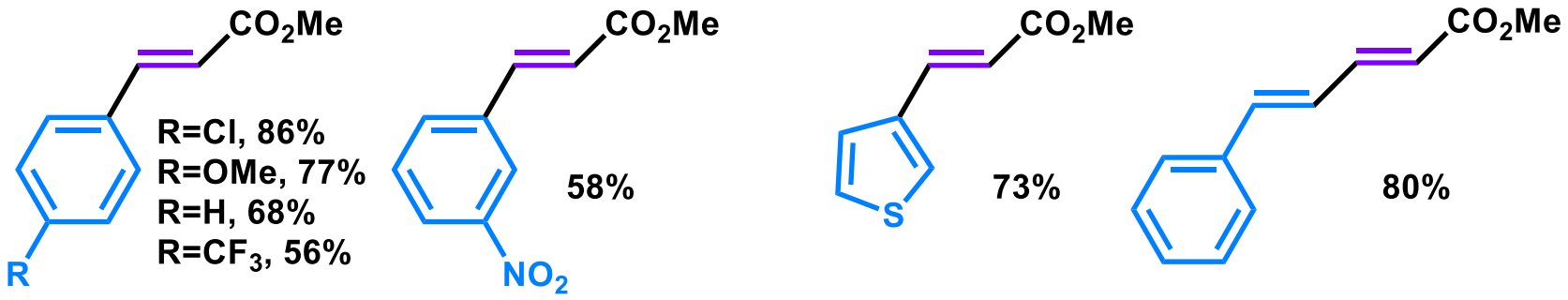


1) Merad, J.; Grant, P.;Stopka, T.; Sabbatani, J.; Meyrelles, R.; Preinfalk, A.; Matyasovsky, J.; Maryasin, B.; Gonzalez, L.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 12536.

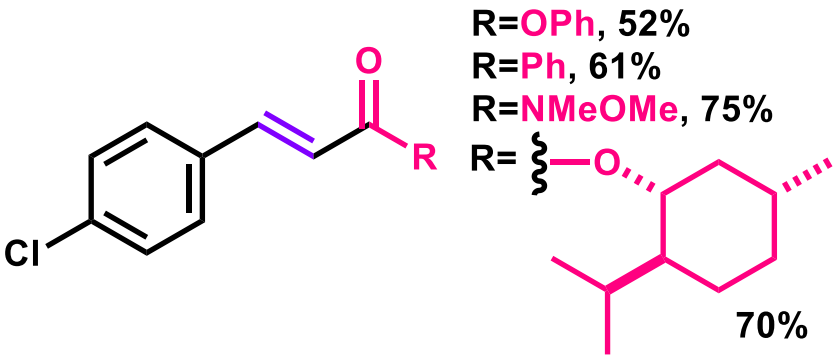
Substrate Scope of E-Selective Olefination

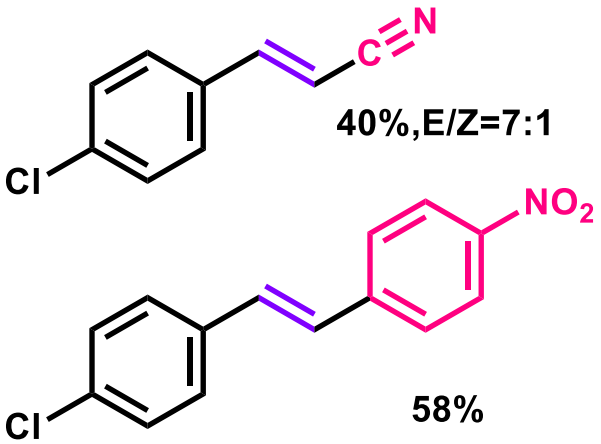


Tosyl imine scope



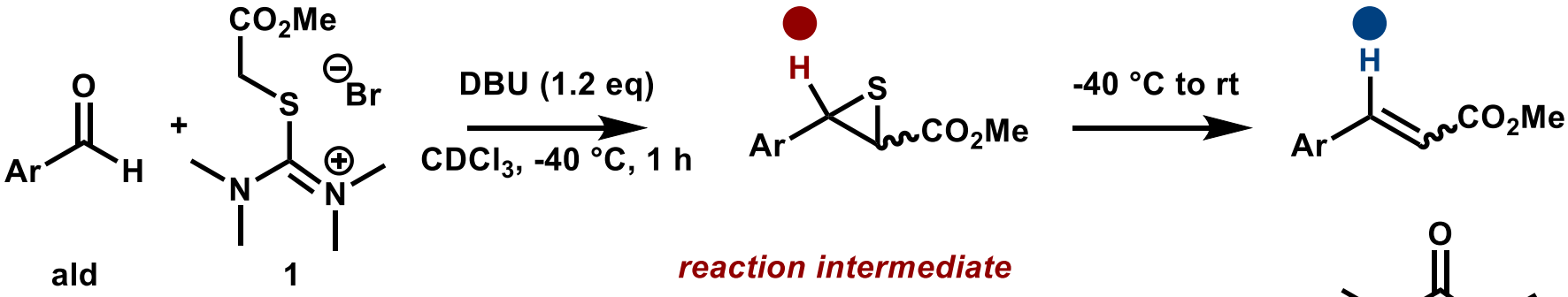
Isothiouronium scope





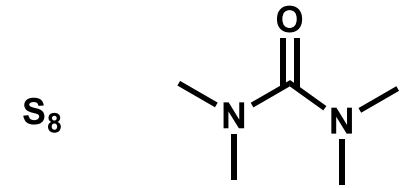
1) Merad, J.; Grant, P.;Stopka, T.; Sabbatani, J.; Meyrelles, R.; Preinfalk, A.; Matyasovsky, J.; Maryasin, B.; Gonzalez, L.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 12536.

Mechanistic Study

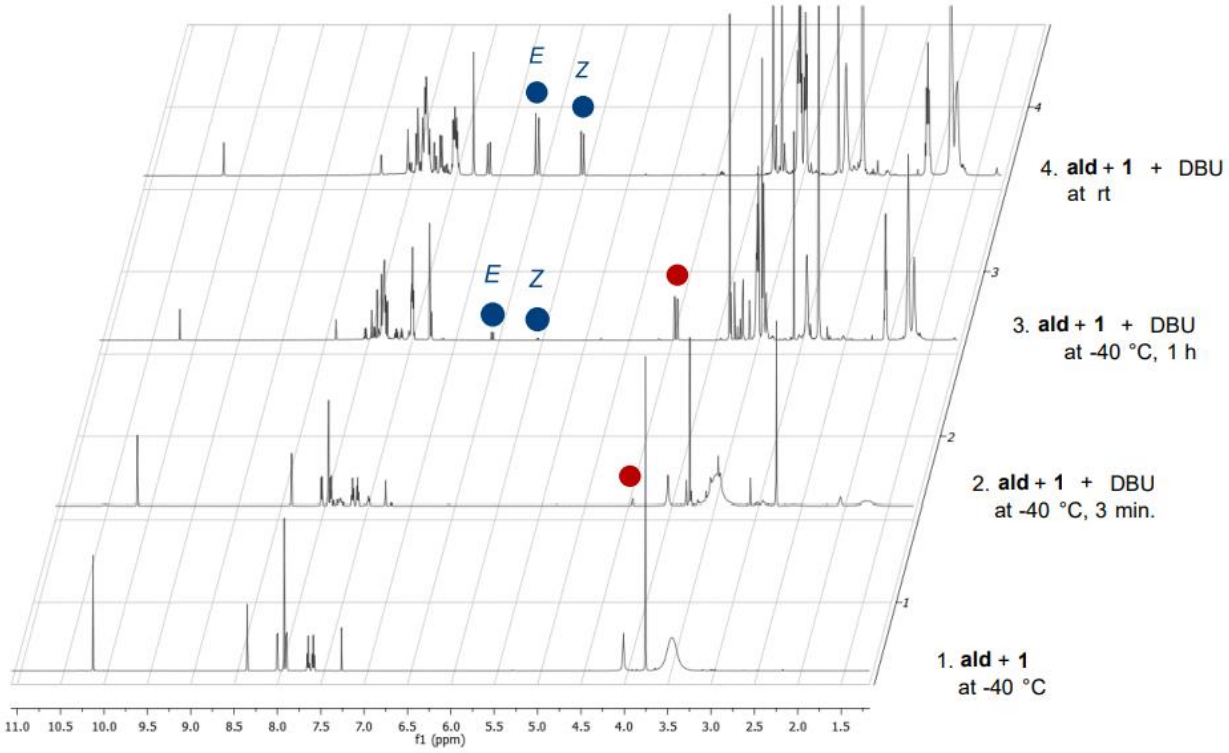


ald 1

reaction intermediate

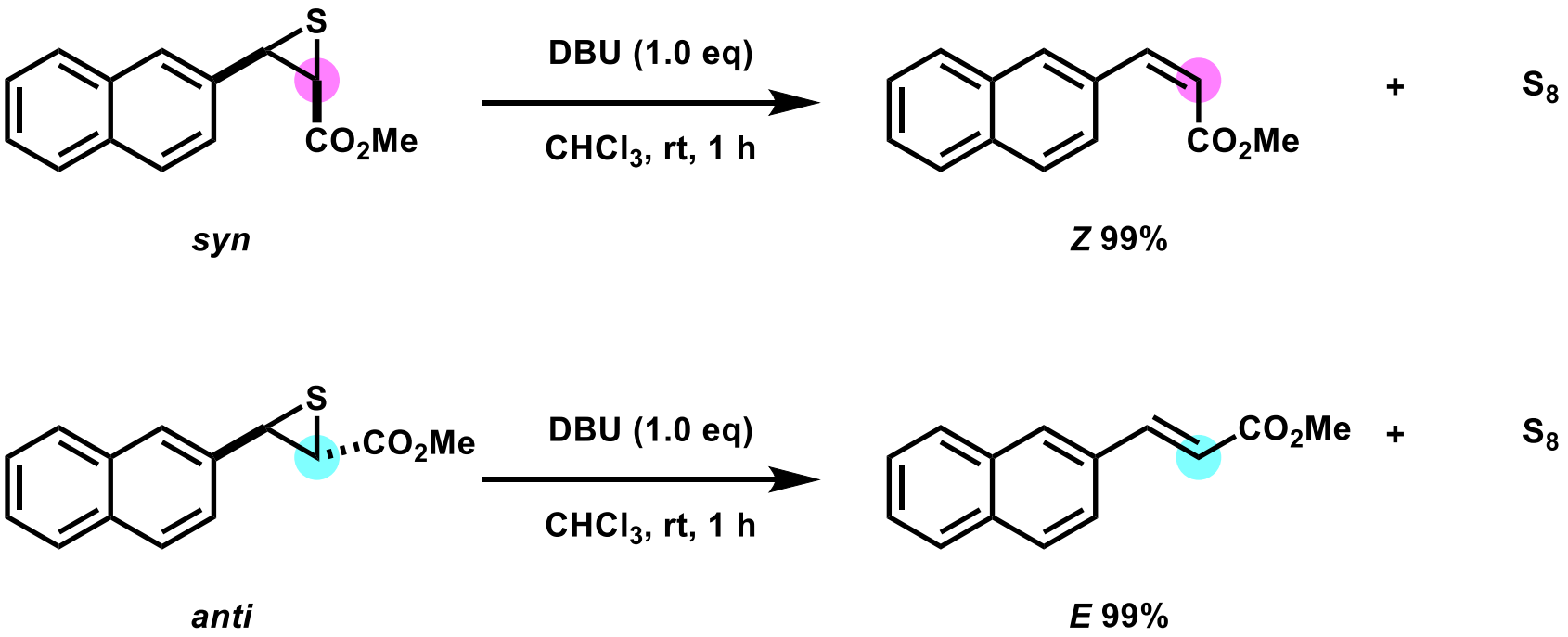


These end-products were detected



1) Merad, J.; Grant, P.;Stopka, T.; Sabbatani, J.; Meyrelles, R.; Preinfalk, A.; Matyasovsky, J.; Maryasin, B.; Gonzalez, L.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 12536.

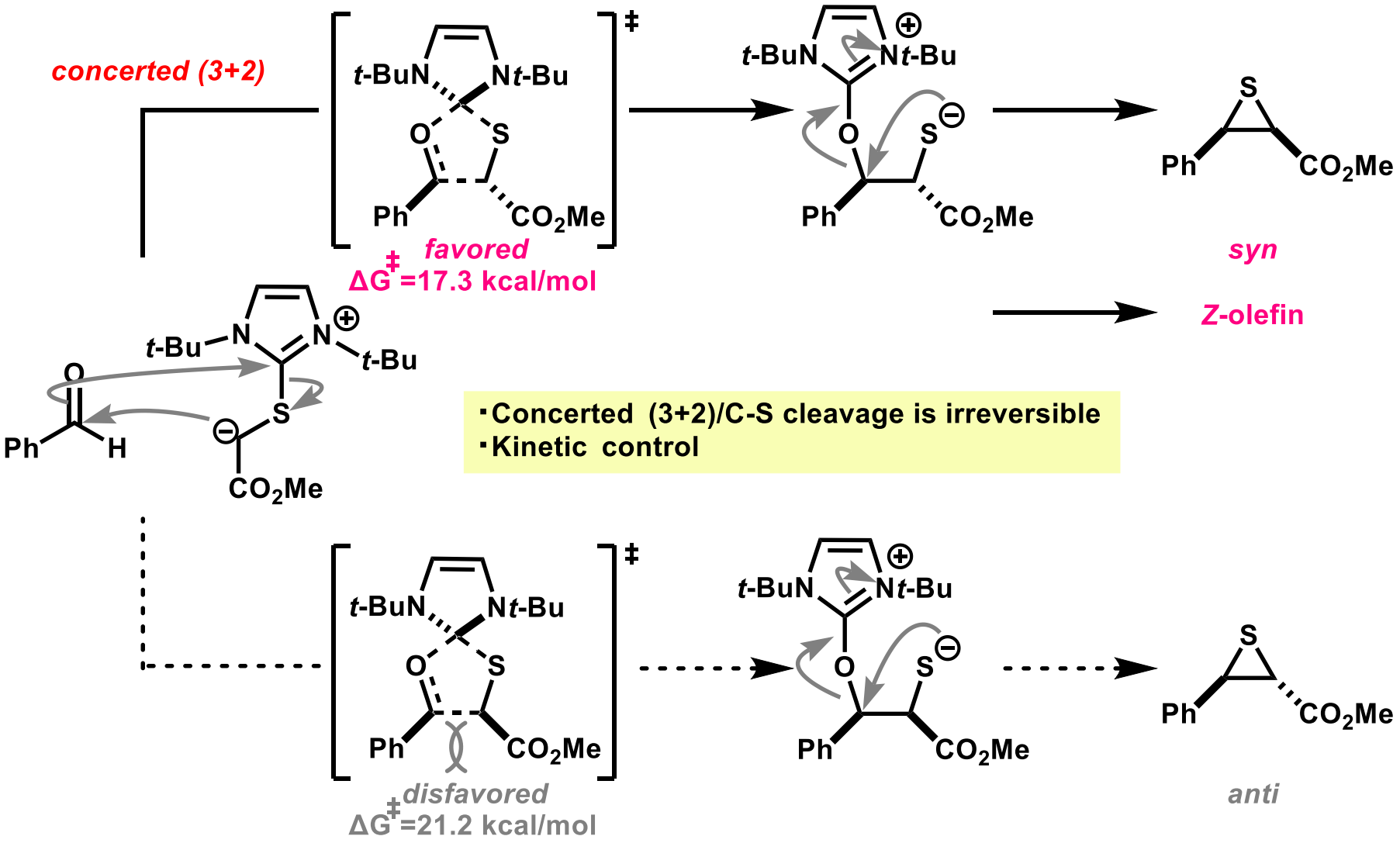
Stereospecificity of Desulfurisation



Desulfurisation prodeeds stereospecificly.
→The selectivity of olefination is determined by the stereochemsitry of episulfide, the reaction intermediate.

1) Merad, J.; Grant, P.;Stopka, T.; Sabbatani, J.; Meyrelles, R.; Preinfalk, A.; Matyasovsky, J.; Maryasin, B.; Gonzalez, L.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 12536.

Z-Selective Olefination via *syn*-Episulfide

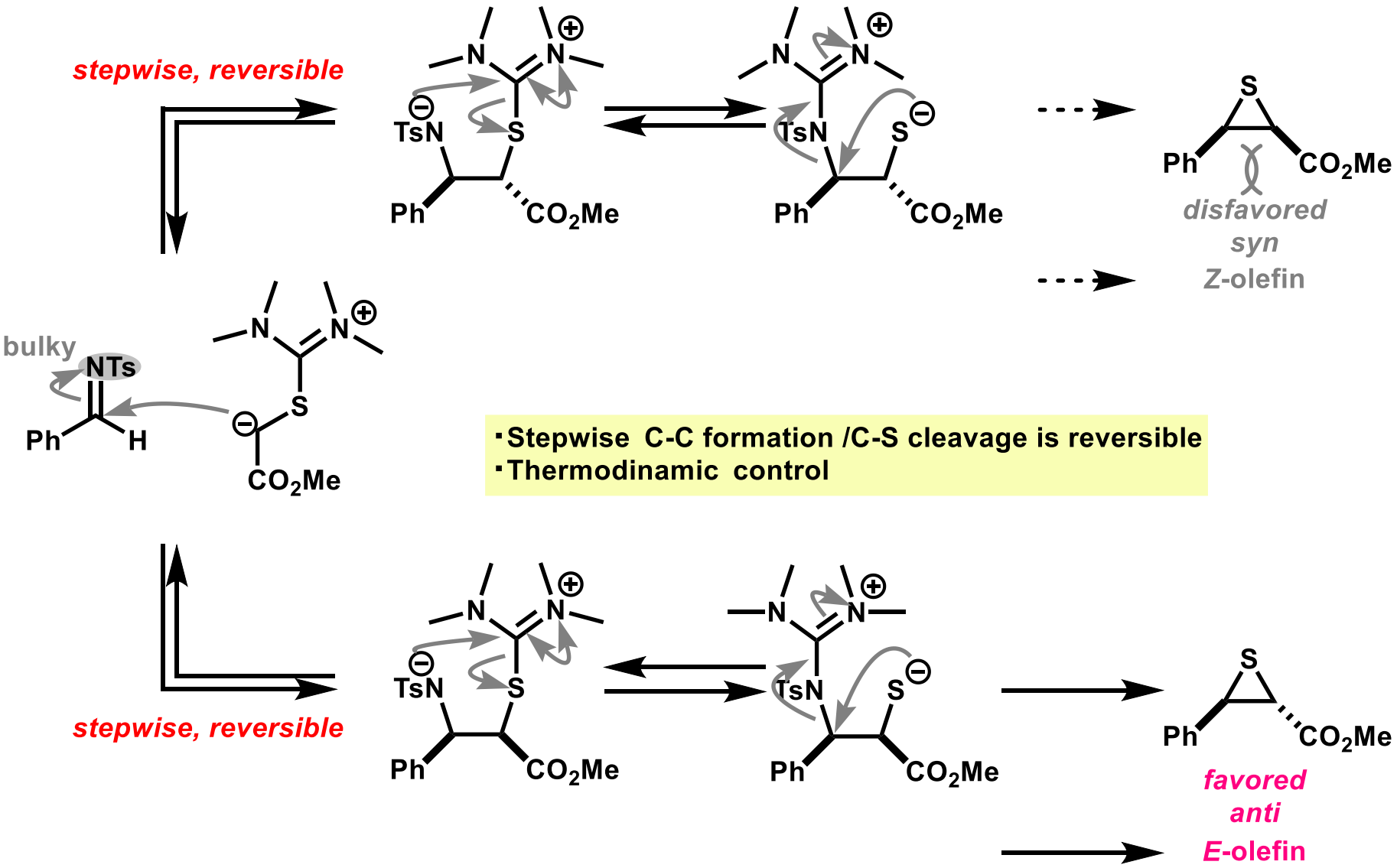


- Concerted (3+2)/C-S cleavage is irreversible
- Kinetic control

Calculations were conducted at PBE0-D3BJ/def2-TZVP,SMD//PBE0-D3BJ/def2-SVP,SMD level of theory

1) Merad, J.; Grant, P.;Stopka, T.; Sabbatani, J.; Meyrelles, R.; Preinfalk, A.; Matyasovsky, J.; Maryasin, B.; Gonzalez, L.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 12536.

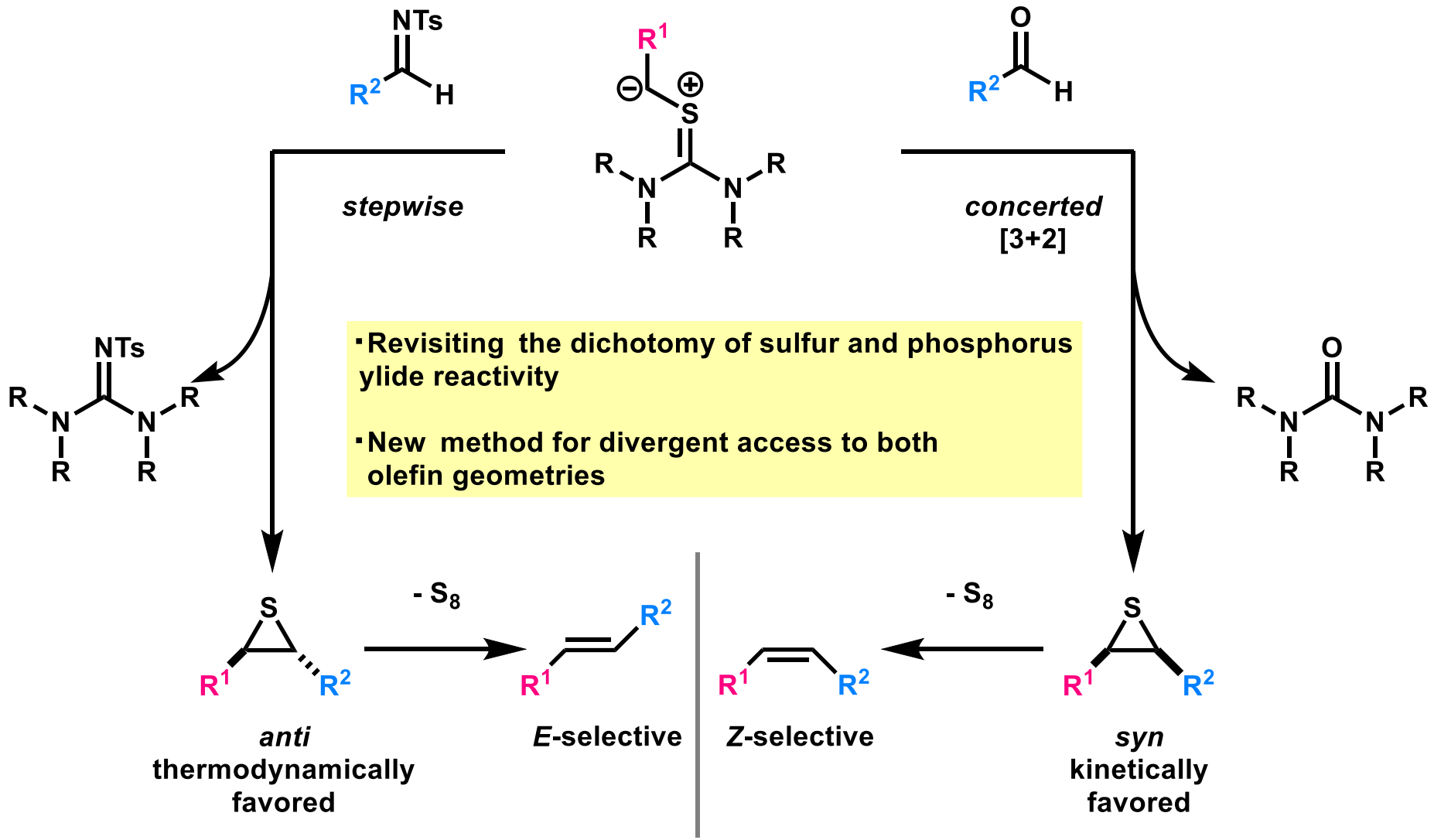
E-Selective Olefination via *anti*-Episulfide



- Stepwise C-C formation /C-S cleavage is reversible
- Thermodinamic control

1) Merad, J.; Grant, P.;Stopka, T.; Sabbatani, J.; Meyrelles, R.; Preinfalk, A.; Matyasovsky, J.; Maryasin, B.; Gonzalez, L.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 12536.

Summary 2



1) Merad, J.; Grant, P.;Stopka, T.; Sabbatani, J.; Meyrelles, R.; Preinfalk, A.; Matyasovsky, J.; Maryasin, B.; Gonzalez, L.; Maulide, N. *J. Am. Chem. Soc.* **2022**, *144*, 12536.